<Division of Synthetic Chemistry>Synthetic Organic Chemistry

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– Synthetic Organic Chemistry –

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Scope of Research

The research interests of this laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the following areas: 1) asymmetric alkylation of carbonyl compounds based on “memory of chirality”, 2) organocatalysis for fine organic syntheses, 3) synthesis of unusual amino acids and nitrogen heterocycles, 4) regioselective functionalization of carbohydrates, and 5) the structural and functional investigation of heterochiral oligomers.

KEYWORDS

Organocatalysis
Regioselective Functionalization
Dynamic Chirality
Unusual Amino Acid
Molecular Recognition

Selected Publications

Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K., Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chirality at Ambient Temperature, *J. Am. Chem. Soc.*, **130,** 4153-4157 (2008).

Kawabata, T.; Jiang, C.; Hayashi, K.; Tsubaki, K.; Yoshimura, T.; Majumdar, S.; Sasamori, T.; Tokitoh, N., Axially Chiral Binaphthyl Surrogates with an Inner N-H-N Hydrogen Bond, *J. Am. Chem. Soc.*, **131,** 54-55 (2009).

Yoshida, K.; Furuta, T.; Kawabata, T., Organocatalytic Chemoselective Monoacylation of 1, *n*-Linear Diol, *Angew. Chem. Int. Ed.*, **50,** 4888-4892 (2011).

Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T., Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts, *Angew. Chem. Int. Ed.*, **52,** 8093-8097 (2013).

Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T., Asymmetric α-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates via Momory of Chirality, *J. Am. Chem. Soc.*, **135,** 13294-13297 (2013).

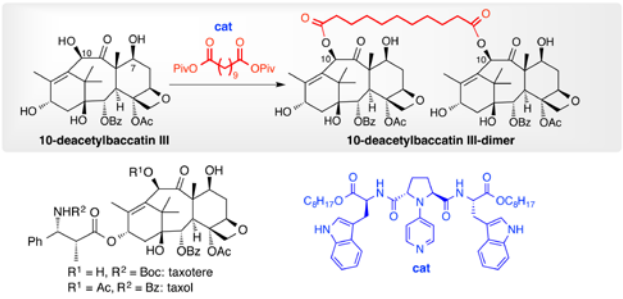
Yoshimura, T.; Tomohara, K.; Kawabata, T., Asymmetric Induction via Short-Lived Chiral Enolates with Chiral C-O Axis, *J. Am. Chem. Soc.*, **135**, 7102-7105 (2013).

Takeuchi, H.; Mishiro, K.; Ueda, Y.; Fujimori, Y.; Furuta, T.; Kawabata, T., Total Synthesis of Ellagitannins via Regioselective Sequential Functionalization of Unprotected Glucose, *Angew. Chem. Int. Ed.*, **54,** 6177-6180 (2015).

Ueda, Y.; Furuta, T.; Kawabata, T., Final-Stage Site-Selective Acylation for the Total Syntheses of Multifidosides A-C, *Angew. Chem. Int. Ed.*, **54,** 11966-11970 (2015).

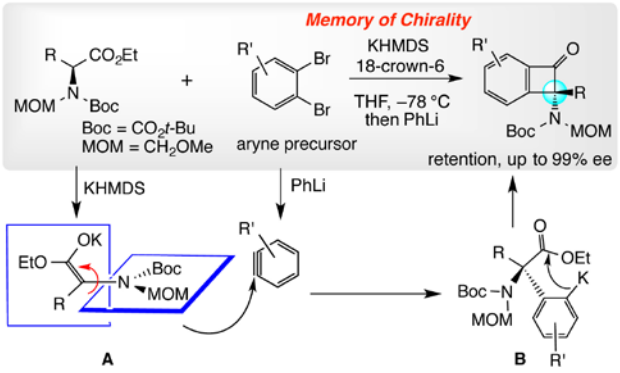
Late-stage Functionalization of Natural Products by Organocatalysis: Site-Selective Dimerization of 10-Deacetylbaccatin III

Late-stage site-selective functionalization of biologically active compounds has been receiving increasing attention because it enables diversification of biologically active compounds retaining their original activity. Here, we report application of our strategy for organocatalytic site-selective acylation to dimerization of 10-deacetylbaccatin III. 10-Deacetylbaccatin III is a natural terpenoid available in a relatively abundant amount and used as a key intermediate for clinically widely used antitumor agents, taxol and taxotere. Dimerization of bioactive compounds is potentially useful strategy toward the discovery of the agents with improved activity profiles including promising activity against the native-compound-resistant infections and cancers. The organocatalytic site-selective acylation of 10-Deacetylbaccatin III with a mixed anhydride prepared from undecanedioic acid and pivaloyl chloride took place at C(10)-OH in the presence of an organocatalyst to provide its dimer as a pure regioisomer in 40% yield. The site-selectivity was assumed to be controlled by the catalyst because the C(7)-OH has been known to be intrinsically more reactive hydroxy group.



Asymmetric α-Arylation of α-Amino Acid Derivatives via Memory of Chirality

We have studied asymmetric synthesis via memory of chirality (MOC). A salient feature of the MOC strategy is that asymmetric reactions take place via axially chiral enolates with limited half-lives of racemization. Because the rate of enolate-racemization strongly depends on the reaction temperature, the reactions via MOC are usually performed at low temperatures to minimize the enolate racemization. While we have successfully developed several intermolecular asymmetric reactions and *intramolecular* asymmetric α-arylation of α-amino acid derivatives via the MOC strategy, the development of asymmetric *intermolecular α-arylation* has been unsuccessful so far. This was assumed to be because usual methods for α-arylation of enolates often requires long reaction times at high temperature, which should cause significant racemization of the intermediary chiral enolates. We describe here a solution to this long-standing problem in the MOC study. We employed arynes as reactive electrophilic aryl species at low temperatures, and successfully developed the target reaction. Treatment of a solution of the amino acid derivative and the aryne precursor with potassium hexamethyldisilazide (KHMDS) followed by phenyl lithium (PhLi) at –78 °C gave benozocyclobutenones with tetra-substituted carbon with retention of configuration in up to 99% ee. The reaction was assumed to proceed via intermolecular asymmetric α-arylation of axially chiral enolate **A** generated by the amino acid derivative and KHMDS with arynes generated by the aryne precursors and PhLi, followed by intramolecular C-acylation of resulting aryl metallic species **B**.



Asymmetric Intramolecular C–H Insertion Promoted by Dirhodium(II) Carboxylate Catalyst Bearing Axially Chiral Amino Acid Derivatives

The asymmetric intramolecular C–H insertion of a rhodium carbenoid intermediate has attracted much attention as a powerful synthetic tool for constructing chiral cyclic compounds. A dirhodium(II) carboxylate catalyst bearing axially chiral amino acid derivatives is prepared. This catalyst is effective in the asymmetric intramolecular C–H insertion of α-aryl-α-diazoacetates to α-aryl-β-substituted γ-lactones with a reasonable level of diastereo- and enantioselectivity, especially in the reaction of phenyl and β-naphthyl substituted substrates.